PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To:
KNOBBE, MARTENS, OLSON & BEAR, LLP
Attn. Mallon, Joseph J.
2040 Main Street 14th Floor
Irvine, CA 92614
ETATS-UNIS D'AMERIQUE

	Date of mailing *(day/month/year)* 29/01/2009
Applicant's or agent's file reference NEREUS.160VP	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US2008/062553	International filing date *(day/month/year)* 02/05/2008
Applicant NEREUS PHARMACEUTICALS, INC.	

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41–22) 338.82.70

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL–2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Jens Ambrosch

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
NEREUS.160VP		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2008/062553	02/05/2008	04/05/2007

Applicant

NEREUS PHARMACEUTICALS, INC.

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of:

[X] the international application in the language in which it was filed

[ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**

[ ] the text is approved as submitted by the applicant

[X] the text has been established by this Authority to read as follows:

USE OF [3.2.0] HETEROCYCLIC COMPOUNDS AND ANALOGS THEREOF FOR TREATING INFECTIOUS DISEASES

5. With regard to the **abstract,**

[ ] the text is approved as submitted by the applicant

[X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant

[ ] as selected by this Authority, because the applicant failed to suggest a figure

[ ] as selected by this Authority, because this figure better characterizes the invention

b. [X] none of the figures is to be published with the abstract

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

Disclosed is the use of [3.2.0] heterocyclic compounds, preferably salinosporamide A, for the manufacture of a medicament for treating infectious diseases in an animal. The animal is a mammal, preferably a human or a rodent.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/062553

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/133 A61K31/407 A61K31/4409 A61K31/4965 A61K31/65
A61K31/7036 A61K38/06 A61K45/06 A61P31/00 A61P31/16
A61P31/08 A61P11/00 A61P27/16 A61P1/12 A61P31/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BIOSIS, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/071382 A (BAYER HEALTHCARE AG [DE]; STADLER MARC [DE]; SEIP STEPHAN [DE]; MUELLE) 26 August 2004 (2004-08-26)	1-3,7, 9-12,16, 18
Y	page 3, paragraph 4 - page 4, paragraph 3 page 6, paragraph 4 - page 8, paragraph 1 page 19, last paragraph - page 20, paragraph 2 examples 1-3 page 56, paragraph 4 - last paragraph page 57; table A claims 1-3	4-6,8, 13-15,17

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 January 2009	29/01/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Cielen, Elsie

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 2006/060809 A (NEREUS PHARMACEUTICALS INC [US]; PALLADINO MICHAEL [US]; POTTS BARBARA) 8 June 2006 (2006-06-08) page 5, paragraph 13 - page 6, paragraph 21 page 20, paragraph 126 pages 34-35, paragraph 170 page 51, paragraph 198 - page 52, paragraph 203 page 58, paragraph 218-220 page 72, paragraph 272 pages 72-73, paragraph 274 page 80, paragraph 293 pages 87-88, paragraph 313 page 90, paragraph 320 examples 36,40,51,60,61 pages 191-192, paragraph 538 claims 23,33,34,41,49,51,52	1,6,7,9, 10,15, 16,18 6,8,15, 17
Y	M. O'NEIL: "The Merck Index Thirteenth Edition" 2001, MERCK RESEARCH LABORATORIES , WHITEHOUSE STATION N.J. , XP002510887 pages THER-5, column 3 - pages THER-7, column 2	8,17
Y	M.H. BEERS, R. BERKOW: "The Merck Manual of Diagnosis and Therapy" 1999, MERCK RESEARCH LABORATORIES , WHITEHOUSE STATION N.J. , XP002510943 page 1193, column 2, paragraph 1	4,5,13, 14
Y	US 2004/138196 A1 (FENICAL WILLIAM [US] ET AL FENICAL WILLIAM [US] ET AL) 15 July 2004 (2004-07-15) page 3, paragraph 51	1,2,6, 9-11,15, 18
Y	WO 2005/094423 A (HARVARD COLLEGE [US]; GOLDBERG ALFRED L [US]) 13 October 2005 (2005-10-13) page 1, paragraph 3 pages 4-5, paragraph 12 page 9, paragraph 29 - page 10, paragraph 33 claims 1,6-8	1-18
Y	US 2005/203029 A1 (SCHUBERT ULRICH [DE] ET AL) 15 September 2005 (2005-09-15) page 7, paragraphs 67,68 page 8, paragraph 72 page 9, paragraph 109 claims 44,45,48,51,53	1,6-10, 15-18

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SCHIEWE H (REPRINT) HAUSTEDT L O ET AL: "Rational approaches to natural-product-based drug design" CURRENT OPINION IN DRUG DISCOVERY & DEVELOPMENT, (JUL 2006) VOL. 9, NO. 4, PP. 445-462. ISSN: 1367-6733. PB - THOMSON SCIENTIFIC, MIDDLESEX HOUSE, 34-42 CLEVELAND STREET, LONDON, W1T 4JE, ENGLAND., July 2006 (2006-07), XP008100461 page 455, column 2, paragraph 2 figure scheme10	1-18
A	NICOLAUS B J R: "Symbiotic Approach to Drug Design" DECISION MAKING IN DRUG RESEARCH, XX, XX, 1 January 1983 (1983-01-01), pages 173-186, XP002197412	
P,Y	WO 2007/138116 A (VIROLOGIK GMBH [DE]; SCHUBERT ULRICH [DE]) 6 December 2007 (2007-12-06) page 1, paragraph 1 pages 4-5, paragraph 16 page 6, paragraphs 20,21 pages 7-9, paragraph 24 claims 20,21,26-29,35	1,2, 6-11, 15-18
T	PRUDHOMME, JACQUES ET AL: "Marine actinomycetes: a new source of compounds against the human malaria parasite" PLOS ONE , 3(6), NO PP. GIVEN CODEN: POLNCL; ISSN: 1932-6203 URL: HTTP://WWW.PLOSONE.ORG/ARTICLE/INFO%3ADOI%2F10.1371%2FJOURNAL.PONE.00 02335, 2008, XP008100452 abstract page 2, column 1, paragraph 3 page 3, column 2, last paragraph - page 4, column 1, paragraph 1	1,6,9, 10,15,18

4

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/062553

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004071382 A	26-08-2004	AU 2004212296 A1	26-08-2004
		BR PI0407234 A	31-01-2006
		CA 2515940 A1	26-08-2004
		JP 2006517934 T	03-08-2006
		KR 20050098928 A	12-10-2005
		MX PA05008478 A	18-10-2005
		US 2006229353 A1	12-10-2006
WO 2006060809 A	08-06-2006	AU 2005311572 A1	08-06-2006
		CA 2590334 A1	08-06-2006
		EP 1835910 A2	26-09-2007
		JP 2008522975 T	03-07-2008
		KR 20070086895 A	27-08-2007
US 2004138196 A1	15-07-2004	US 2004259856 A1	23-12-2004
WO 2005094423 A	13-10-2005	NONE	
US 2005203029 A1	15-09-2005	AU 2003223913 A1	20-10-2003
		WO 03084551 A1	16-10-2003
		DE 10316735 A1	20-11-2003
		DE 10391147 D2	17-02-2005
		EP 1492545 A1	05-01-2005
WO 2007138116 A	06-12-2007	DE 102006026464 A1	06-12-2007

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2008/062553	02.05.2008	04.05.2007

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/133 A61K31/407 A61K31/4409 A61K31/4965 A61K31/65 A61K31/7036 A61K38/06 A61K45/06 A61P31/00 A61P31/16 A61P31/08 A61P11/00 A61P27/16 A61P1/12 A61P31/06 A61P13/02 A61P31/04

Applicant
NEREUS PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Paye Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	see form PCT/ISA/210	Cielen, Elsie Telephone No. +31 70 340-4540

Form PCT/ISA/237 (Cover Sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2008/062553

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1-5, 7-14, 16-18 (all partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 1-5, 7-14, 16-18 (all partially)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	4, 5, 8, 13, 14, 17
	No: Claims	1-3, 6, 7, 9-12, 15, 16, 18
Inventive step (IS)	Yes: Claims	-
	No: Claims	1-18
Industrial applicability (IA)	Yes: Claims	1-18
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.i. This application does not meet the requirements of Article 5 and 6 PCT, because claims 1-5, 7-14 and 16-18 are not clear, nor sufficiently supported and the invention is not sufficiently disclosed by the description.

(a) Present claims 1-5, 7-14 and 16-18 relate to a very large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of claims 6 and 15, and to formulae I and II wherein E1 and E3 are both O, which is a generalisation of all the exemplified compounds.

(b) Moreover, present claims 1-5, 7-14 and 16-18 relate to compounds which actually are not well-defined. The use of the definition "pro-drug thereof" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the compounds as specified under item **III.i(a).**

III.ii. No opinion will be given in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT) (see also item **V.i**).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.i.(a) Attention is drawn to the fact that the present statement expressed as to novelty, inventive step and industrial applicability refers only to matter for which an International

Search Report has been drawn up (see item **III**).

(b) Present claims 1-9 relate to a method of treatment. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

V.ii. Reference is made to the following documents:

D1: WO 2004/071382 A (BAYER HEALTHCARE AG [DE]; STADLER MARC [DE]; SEIP STEPHAN [DE]; MUELLE) 26 August 2004 (2004-08-26)

D2: WO 2006/060809 A (NEREUS PHARMACEUTICALS INC [US]; PALLADINO MICHAEL [US]; POTTS BARBARA) 8 June 2006 (2006-06-08)

D3: M. O'NEIL: "The Merck Index Thirteenth Edition" 2001, MERCK RESEARCH LABORATORIES , WHITEHOUSE STATION N.J. , XP002510887

D4: M.H. BEERS, R. BERKOW: "The Merck Manual of Diagnosis and Therapy" 1999, MERCK RESEARCH LABORATORIES , WHITEHOUSE STATION N.J. , XP002510943

D5: US 2004/138196 A1 (FENICAL WILLIAM [US] ET AL FENICAL WILLIAM [US] ET AL) 15 July 2004 (2004-07-15)

D6: WO 2005/094423 A (HARVARD COLLEGE [US]; GOLDBERG ALFRED L [US]) 13 October 2005 (2005-10-13)

D7: US 2005/203029 A1 (SCHUBERT ULRICH [DE] ET AL) 15 September 2005 (2005-09-15)

D8: SCHIEWE H (REPRINT) HAUSTEDT L O ET AL: "Rational approaches to natural-product-based drug design" CURRENT OPINION IN DRUG DISCOVERY & DEVELOPMENT, (JUL 2006) VOL. 9, NO. 4, PP. 445-462. ISSN: 1367-6733. PB - THOMSON SCIENTIFIC, MIDDLESEX HOUSE, 34-42 CLEVELAND STREET, LONDON, W1T 4JE, ENGLAND., July 2006 (2006-07), XP008100461

D9: NICOLAUS B J R: "Symbiotic Approach to Drug Design" DECISION MAKING IN DRUG RESEARCH, XX, XX, 1 January 1983 (1983-01-01), pages 173-186, XP002197412

V.iii. Article 33(2) PCT.

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-3, 6, 7, 9-12, 15, 16 and 18 is not new in the sense of Article 33(2) PCT.

(a) Document D1 discloses that compounds which fit in present formula I are proteasome inhibitors (p. 3, par. 4 - p. 4, par. 3; p. 6, par. 4 - p. 8, par. 1; examples 1-3; p. 56, par. 4 - last par.; p. 57, table A; claims 1-3). They can be used for the treatment of fungal, viral and bacterial infections, alone or in combination with other active compounds, and for the treatment of *inter alia* toxic shock syndrome, sepsis, cerebral malaria, tuberculosis and fever (p. 19, last par. - p. 20, par. 2). Therefore, the subject-matter of present claims 1-3, 7, 9-12, 16 and 18 is not novel over D1.

(b) Document D2 discloses the use of the presently claimed compounds, including Salinosporamide A, for the treatment of *inter alia* septic shock, trachoma, and infectious diseases, including Plasmodium and Trypanosoma (par. [0013]-[0021], [0126], [0170], [0198]-[0203], [0218]-[0220], [0313], [0320]; claims 23, 33, 34, 41, 49, 51, 52). Plasmodium is generally known to cause malaria. Optionally, other antimicrobial agents can be coadministered (par. [0293]). The compounds are proteasome inhibitors (par. [0272], [0274]; examples 36, 40, 51, 60, 61; par. [0538]). Therefore, the subject-matter of present claims 1, 6, 7, 9, 10, 15, 16 and 18 is not novel over D2.

V.iv. Article 33(3) PCT.

(a) The problem to be solved by the present application is the provision of alternative medicines for the treatment of specific infectious diseases, preferably tuberculosis.

The proposed solution is the use of [3.2.0] heterocyclic compounds of formulae (I) or (II), preferably salinosporamide A.

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-18 - as far as novel - does not involve an inventive step in the sense of Article 33(3) PCT.

(b) As far as the treatment of tuberculosis is concerned, document D1 can be considered

to represent the closest state of the art (see item **V.iii(a)**).

(i) The subject-matter of present claims 4-5 and 13-14 differs herefrom in that the mycobacteria causing tuberculosis are specified.

This subject-matter does not involve an inventive step, because from D4 it is known that tuberculosis is caused by Mycobacterium tuberculosis, M. bovis or M. africanum (p. 1193, right-hand column, par. 1).

(ii) The subject-matter of present claims 6 and 15 differs herefrom in that Salinosporamide A, which has as R_1 an alkyl chain of different length and substituted by Cl, is used.

The problem to be solved may therefore be regarded as the provision of an alternative proteasome inhibitor for the treatment of the same disease.

The solution proposed in claims 6 and 15 does not involve an inventive step, because the compounds of D1 are disclosed as alternatives to Salinosporamide A (D1: p. 3, last par. - p. 4, par. 1). Moreover, structure-activity relationship investigation of the R_1 side chain has demonstrated that compounds having a good leaving group in the R_1 side chain (as in Salinosporamide A) have increased activity (see D2, example 60, in particular par. [0528]-[0531]).

It was therefore obvious for the skilled person, knowing from D1 that proteasome inhibitors structurally very close to Salinosporamide A can be used for the treatment of tuberculosis and from D2 that compounds having a good leaving group in the R_1 side chain have increased activity, to at least try to use Salinosporamide A for the treatment of tuberculosis with a reasonable expectation of success.

In the absence of comparative data and/or convincing arguments showing a surprising and/or unexpected effect linked to the use of Salinosporamide A instead of the compounds of D1 for the treatment of tuberculosis, an inventive step cannot be recognised at present.

(iii) The subject-matter of present claims 8 and 17 differs from D1 in that specific anti-infective agents are coadministered. This subject-matter does not involve an inventive step because from D3 it is known that these compounds are antibacterial or even tuberculostatic agents (p. THER-5, column 3 - p. THER-7, column 2).

(c) Furthermore, even if novelty could be restored, the present application would very likely lack an inventive step over D2, which clearly teaches the use of compounds of formulae I and II, including Salinosporamide A, for several of the presently claimed infectious diseases, optionally in combination with further antimicrobial agents (see item **V.iii(b)**).

(d) The present application also lacks an inventive step over each of D6-D7.

Document D6 discloses the treatment of bacterial infections, such as Mycobacterium tuberculosis, Mycobacterium leprae, Clostridium perfringens, Listeria monocytogenes, Staphylococcus aureus, Staphylococcus epiderm, Streptococcus mutans, Streptococcus pneumoniae, Brucella, Campylobacter, Escherichia coli, Gardnerella vaginalis, Haemophilius influenziae, Heliobacter pylori, Salmonella enteridis, Salmonella typhi, Shigella boydii, Streptococcus pyogenes, Yersinia enterocolitica, Yersinia pestis, Chlamydia psittaci, Chlamydia trachomatis, Mycoplasme pneumoniae and Ehrlichia chafensis, preferably Mycobacterium tuberculosis, with a peptide compound which selectively inhibits bacterial proteasomes (par. [003], [012], [029]-[033]; claims 1, 6-8).

Document D7 teaches that proteasome inhibitors, optionally in combination with other antiviral agents, such as clastolactacystein beta-lactone (=omuralide) or PS-519, are used for the treatment of virus infections by Flaviviridae or Pestivirus, such as diarrheal diseases (par. [0067]-[0068], [0109]; claims 44, 45, 48, 51 and 53).

The subject-matter of present claims 1-18 differs herefrom in that alternative proteasome inhibitors are used.

The problem to be solved may therefore be regarded as the provision of an alternative proteasome inhibitor for the treatment of specific infectious diseases.

The solution proposed in claims 1-18 - as far as novel - does not involve an inventive step, because Salinosporamide A is known to be an exceptionally high and selective inhibitor of proteasomes, more potent than omuralide and PS-519 (see e.g. D8, p. 455, right-hand column, par. 2).

It was therefore obvious for the skilled person, knowing from each of D6 and D7 that proteasome inhibitors can be used for the treatment of the claimed infectious diseases and from e.g. D8 that Salinosporamide A is an exceptionally high and selective inhibitor of proteasomes, to at least try to use Salinosporamide A for the treatment of the claimed infectious diseases with a reasonable expectation of success.

In the absence of comparative data and/or convincing arguments showing a surprising and/or unexpected effect linked to the use of Salinosporamide A instead of the compounds of D6 and D7 for the treatment of the claimed infectious diseases, an inventive step cannot be recognised at present.

(e) Moreover, it appears that the problem underlying the application has not been solved over the whole of the scope of the claims: Document D5 states on p. 3 , par. [0051] and in

example 2 that "Salinosporamide A ... shows little antifungal activity against *C. albicans* and no antibacterial activity (*S. aureus, E. faecium*)."

In this respect, it is to be noted that the only pharmacological data relate to the treatment of tuberculosis (example 36-37). The latter example contains a mere statement, without any real data. Example 43 relates to antimicrobial assays for a variety of infectious diseases, but does not contain any data.

A positive opinion on inventive step can be given only if and as far as the problem underlying the application actually is solved by all claimed variants.

(f) Claims 1-5, 7-14 and 16-18 of the present application relate to a very wide variety of compounds which all are supposed to be effective in the treatment of the claimed infectious diseases (see also items **III.I(a)** and **VIII**).

By virtue of the many possible substituents, which in themselves at least in part will represent further pharmacophoric moieties, it appears to be highly questionable that it is predictable that all claimed variants actually will exhibit the claimed properties in relation to the treatment of the sepcific infectious diseases. The skilled person is aware of the fact that the effects of such hybrid compounds comprising more than one pharmacophoric group cannot be foreseen having regard to the preparation of a medicament for the claimed therapeutic utility (see also D9). The presence of an inventive step can only be recognised for problems which have been solved by all claimed variants.

Re Item VI

Certain documents cited

The examination has been carried out assuming that the priority of the application is valid. However, attention is drawn to the fact that the document which has been cited in the search report as "P" document, namely WO2007138116, may become relevant in the national/regional examination phase.

Re Item VIII

Certain observations on the international application

Claims 1-5, 7-14 and 16-18 of the present application relate to a very wide variety of compounds which all are supposed to be effective in the treatment of a very large number of infectious diseases (see also items **III.i(a)** and **V.iv(f)**).

In fact, the number of claimed variants cannot be estimated without undue burden and in any case appears to be fully disproportionate to what actually is disclosed and supported by pharmacological evidence, namely the use of Salinosporamide A for the treatment of tuberculosis (example 36-37). (see also item **V.iv(e)**).

As a rule, protection conferred by a patent should be commensurate with the range of compounds for which the effect has been properly demonstrated, including obvious variants thereof. Having to construe the numerous variants comprised in claims 1-5, 7-14 and 16-18 and to form an opinion on whether or not any one of them has anti-infective activity against one of the claimed diseases imposes a severe and undue burden on the skilled person. It follows that the present application as it stands falls foul of the clear provisions of Articles 5 and 6 PCT.